67th Meeting of Blood Products Advisory Committee
September 15, 2000

Classification of HLA Devices

Presentations

1. Background and presentation of the issues – Sheryl Kochman
2. Third party Review Program – Eric Rechen

Question

1. Does the Committee agree that HLA Devices (for use in detecting antibodies to HLA antigens or determining HLA phenotype or genotype) should be classified as Class II devices?

Mailer

1. Summary
2. 21 CFR 660.10 – Additional Standards for Leukocyte Typing Serum
3. 45 FR 51226, August 1, 1980
4. 47 FR 34532, August 10, 1982
5. FDA Classification of Medical Devices (CDRH)
6. Third Party Review Program Information (CDRH)
7. Guidance for Staff, Industry, and Third Parties; Implementation of Third Party Programs Under the FDA Modernization Act of 1997 (CDRH)
8. Draft Revised Guidance for Staff, Industry, and Third Parties; Implementation of Third Party Programs Under the FDA Modernization Act of 1997 (CDRH)

Classification of HLA Devices
FDA Introduction & Background

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Objectives

- Provide an overview of the current regulatory status of HLA devices
- Provide background regarding medical device classification
- Provide an overview of the Third Party Review Program

What are "HLA Devices"?

- In vitro diagnostic reagents and kits for use in determining the HLA phenotype or genotype of an individual or for detecting and identifying antibodies to HLA antigens

What are "HLA Devices"? (cont'd)

- characterized polyclonal or monoclonal antibodies for determination of phenotype
  - » analogous to Blood Grouping Reagents
    - ◆ (CBER licensed IVD)
- DNA-based assays for determination of genotype
- characterized leukocytes for detection and identification of antibodies
  - » analogous to Reagent Red Blood Cells
    - ◆ (CBER licensed IVD)

What are NOT "HLA Devices"?

- In vitro diagnostic reagents or kits used to predict disease
  - Anti-HLA-B27 to detect HLA-B27 antigen as a marker for ankylosing spondylitis
    - »regulated by Center for Devices and Radiological Health (CDRH)

Regulatory History

- First product license for Leukocyte Typing Serum issued December 1974
- FDA Guidelines for Production, Testing, and Lot Release of Leukocyte Typing Sera issued December 1977
- FDA Proposed Rule recommending that additional standards for Leukocyte Typing Serum be revoked issued August 1, 1980
- FDA Final Rule revoking additional standards for Leukocyte Typing Serum issued August 10, 1982

Effect of Proposed and Final Rules

- Expanded control authority under the Medical Device Amendments to the FD&C Act
  - adulteration §501
  - misbranding §502
  - registration §510
  - classification §513
  - banned devices §516
  - notifications & other remedies §518
  - records & reports §519
  - restrictions on sale, distribution, or use §520(e)
  - good manufacturing practice §520(f)

Effect of Proposed and Final Rules

- All manufacturers (previously licensed and new unlicensed) to register and list under 21 CFR 807
- New manufacturers to submit premarket notification submission (510(k)) per 21 CFR 807
- Labeling to conform to 21 CFR 809.10
- Manufacturing to conform to 21 CFR 820 (cGMP) (currently QSR)
- Classification to follow

Subsequent Regulatory Process

- CBER received, reviewed, and cleared a number of 510(k) submissions (~65)
  - letters variably refer to device as Class I and Class II despite lack of formal classification
  - current letters list device as unclassified

Basis for Confusion

- Proposed rule clearly states a request for classification has been made and will be published upon receipt.
- Also states:
  - If this proposal is published in final form, the device shall be subject to the general controls provisions
  - The agency believes that these and other general controls applicable to medical devices are sufficient
  - The appropriate regulatory status of the product will be considered in the course of classification

Problems Associated With Lack of Classification

- Confusion in industry about which standards apply
- Confusion in CBER about what review criteria apply
- Erroneous belief in industry that registration, listing, and 510(k) submission are not needed
- Confusion in ORA about whether or not to inspect and what standards to apply during an inspection
- Inability to proceed with initiatives pertaining to FDAMA, e.g., Third Party Review

Device Classification Preamendments Devices

- Preamendments devices are those which were on the market prior to enactment of the Medical Device Amendments of 1976
- Three Classes
  - Class I
  - Class II
  - Class III

Class I

- General controls alone are sufficient to provide reasonable assurance of safety and effectiveness **OR**
- It is unclear if general controls alone are sufficient to provide reasonable assurance of safety and effectiveness but the device is not life-supporting, life-sustaining, or of substantial importance in preventing impairment of human health.

General Controls

- Establishment registration
- Product listing
- Conformance to QSR (formerly GMP)
- Conformance to device labeling requirements
- Submission of a 510(k) (if applicable)
- Others in the act

Class I

- Most Class I devices are now exempt from the requirement to submit a 510(k)
  - Those that are not, are designated as "reserved"
- Most Class I devices are not subject to the design control provisions of the QSR
- Some Class I devices are exempt from other requirements of the QSR
- **Least stringent regulatory category**
- EXAMPLE: Blood grouping view box

Class II

- General controls alone are insufficient to provide reasonable assurance of safety and effectiveness and there is sufficient information to establish special controls

Special Controls

- Performance standards
- Special labeling requirements
- Guidance documents
- Recommendations
- Patient registries
- Post-market surveillance
- "Other actions deemed appropriate by the Commissioner"
- **In addition to General Controls**

Class II

- Generally moderate-risk devices
- May be life-supporting or life-sustaining
- Some have been exempted from the requirement to submit a 510(k)
- EXAMPLE: Automated blood grouping and antibody test system

Class III

- There is insufficient information that general or special controls will provide reasonable assurance of safety and effective **AND**
- The device is:
  - life-supporting, life-sustaining, or of substantial importance in preventing impairment of human health **OR**
  - presents a potential unreasonable risk of illness or injury

Premarket Approval

- Manufacturer must submit a premarket approval application (PMA)
  - scientific and regulatory review ensure the safety and effectiveness of the device

Class III

- High risk device
- Most stringent regulatory category
  - General Controls also apply
- EXAMPLE: Electromagnetic blood and plasma warming device

Device Classification Postamendments Devices

- Postamendments devices are those which are introduced to the market after enactment of the Medical Device Amendments of 1976
- Two routes to classification
  - same regulatory class as the device to which it is deemed substantially equivalent
  - Class III if not substantially equivalent to a device already legally on the market

Substantial Equivalence

- The device has the same intended use as the predicate device **AND**
  - The device has the same technological characteristics as the predicate device
    OR
  - The device has different technological characteristics but does not raise new concerns of safety and effectiveness.